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International Bureau

<p>(51) International Patent Classification 6 : C12N 15/12, C07K 14/705, 16/28, G01N 33/50, C12N 15/62, G01N 33/53, C12Q 1/68</p>	A2	<p>(11) International Publication Number: WO 99/32627 (43) International Publication Date: 1 July 1999 (01.07.99)</p>
<p>(21) International Application Number: PCT/US98/27400 (22) International Filing Date: 23 December 1998 (23.12.98) (30) Priority Data: 60/068,690 23 December 1997 (23.12.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/068,690 (CIP) Filed on 23 December 1997 (23.12.97) (71) Applicant (for all designated States except US): THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SAMELSON, Lawrence, E. [US/US]; 6707 East Avenue, Chevy Chase, MD 20815 (US). ZHANG, Weiguo [-US]; 259 Congressional Lane #410, Rockville, MD 20852 (US).</p>	<p>(74) Agents: CARROLL, Peter, G. et al.; Medlen & Carroll, LLP, Suite 2200, 220 Montgomery Street, San Francisco, CA 94104 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: THE PROTEIN TYROSINE KINASE SUBSTRATE LAT AND ITS USE IN THE IDENTIFICATION OF (ANT)AGONISTS OF THE KINASE</p>		
<pre> human LAT 1 MREAILVPCVLGLLLLPIL.AMLHALCVKHCHRLPGSDSTSEDSLPROI 49 murine LAT 1 MEADALSFVGLOGLLLPLPLVTLLAALCVRCRELPVSDSTSTESLPRSI 50 50 QFERPHTVAPNPFA..PPVTSYFPFLSQPDLLPIRSPQPLOGSERTPSS 97 51 LIKPQQITVPRTPAVEPLVTSFFPLRQPDLLPIRSPQPLOGSHRPSS 100 98 RRDSGDANSVASENTERPACE..DADEDEDDEHPNGLVVLPDSTPATST 145 101 QQNSDDANSVASERQEPACKNVDADEDEDDEPN.GLVVLPDSSPAAVP 149 146 AAPSA PALSTFGIRDSAFSMESIDDVVNPVSQGESASASLDGSREVNYS 195 150 VVSSAPVPSNPDLQDSAPSVESCEDVVNPVSESESASASLDGSREVNYS 199 196 QELHPGAAKTEPAALSSQAARE.....VEREGAPPENLOQLN 233 200 PEQOP.VTRARLASVHSQVEDEGEERGVDGREAPPENLOQLN 242 </pre>		
<h3>Human (1-233) and Murine LAT Amino Acid Sequence (1-242)</h3>		
<p>(57) Abstract</p> <p>The invention generally relates to compositions and methods for identifying and testing tyrosine kinase signaling pathway agonists and antagonists, and more particularly, methods and compositions for screening compounds and identifying compounds that will modulate the interaction of protein tyrosine kinase substrates with their intracellular ligands, as well as between their intracellular ligands and other members of the signaling pathway.</p>		

CLAIMS

We claim:

1. An isolated polypeptide comprising at least a portion of the amino acid
5 sequence of SEQ ID NO:4.
2. The isolated polypeptide of Claim 1, wherein said portion comprises a region
comprising at least one tyrosine.
- 10 3. The isolated polypeptide of Claim 1, wherein said portion comprises a region
defined by amino acids 28 to 233.
4. A purified antibody which binds specifically to a polypeptide comprising at
least a portion of the amino acid sequence of SEQ ID NO:4.
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5. The purified antibody of Claim 4, wherein said antibody is a polyclonal
antibody.
6. The purified antibody of Claim 4, wherein said antibody is a monoclonal
20 antibody.
7. An isolated polynucleotide encoding the polypeptide comprising the sequence
of SEQ ID NO:4.
- 25 8. The isolated polynucleotide of Claim 7, wherein said polynucleotide comprises
the sequence of SEQ ID NO: 1
9. The isolated polynucleotide of Claim 7, wherein said polynucleotide is
contained on a recombinant expression vector.
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10. The polynucleotide sequence of Claim 9, wherein said expression vector
containing said polynucleotide sequence is contained within a host cell.

11. A polynucleotide sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1.

12. A method of screening a compound, said method comprising:

a) providing, in any order:

i) a peptide comprising at least a portion of the amino acid sequence set forth in SEQ ID NO:4, wherein said portion is capable of binding to a LAT binding ligand;

ii) a LAT binding ligand; and

iii) one or more compounds for screening;

b) mixing, in any order, said peptide, said LAT binding ligand and said one or more compound; and

c) measuring the extent of binding of said peptide to said LAT binding ligand.

13. The method of Claim 12, wherein said LAT binding ligand comprises a tyrosine kinase.

14. The method of Claim 13, wherein said kinase comprises ZAP-70 kinase.

15. The method of Claim 13, wherein said kinase comprises Syk kinase.

16. The method of Claim 12, wherein said peptide is part of a fusion protein.

17. A method for detecting the presence of a portion of the polypeptide having the amino acid sequence set forth in SEQ ID NO:4, said method comprising the steps of:

a) providing in any order:

i) an antibody capable of reacting with a portion of the polypeptide having the sequence set forth in SEQ ID NO:4; and

ii) a sample suspected of containing at least a portion of the polypeptide having the sequence set forth in SEQ ID NO: 4;

- b) combining said antibody and said sample under conditions such that a complex is formed between said antibody and said portion of said polynucleotide; and
- c) detecting said complex.

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18. The method of Claim 17, wherein said antibody is a polyclonal antibody.

19. The method of Claim 17, wherein said antibody is a monoclonal antibody.

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20. The method of Claim 17, wherein said sample comprises lymphocytes.

21. A method for detecting the presence of polynucleotide sequences encoding at least a portion of LAT gene in a sample, said method comprising the steps of:

- a) providing in any order:
 - i) a polynucleotide comprising a sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO:1; and
 - ii) a sample suspected of containing nucleic acid comprising the sequence of SEQ ID NO:1;
- b) combining said polynucleotide and said sample under conditions such that a hybridization complex is formed between said polynucleotide and said sample nucleic acid; and
- c) detecting said hybridization complex.

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22. The method of Claim 21, wherein said sample nucleic acid is RNA.

23. The method of Claim 21, wherein said sample nucleic acid is DNA.

24. The method of Claim 21, wherein said sample comprises lymphocytes.

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25. The method of Claim 24, wherein said detected hybridization complex correlates with expression of the LAT gene in said lymphocytes.

1 ctaggctttt gcaaaaagct tcacgtgcc gcaagcactc agggcgcaag ggctgctaaa
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Human Vav Nucleotide Sequence (1-2757)

Figure 11A

1 mnvsywaiwt renasakrkq flclknirtf lsccekfgl krsel feafd lfdvqdfgkv
61 iytsalswt piaqngimp spteesvgd ediysglsdq iddtveeded lydcveneea
121 egdeiyedlm rsepvsmpk mteydkrecc lreiqqteek ytdtlgsiqq hflkplqrfl
181 kpqdieiifi niedllrvht hflkemkeal gtpgapnlyq vfikykerfl vygrycsqve
241 saskhldrva aaredvqmkl eecsqrang rftarpadga yaassqispp spgagethag
301 gdgarklrla ldamrdlaqc vnevkrndet lrqitnfqls ienldqslah ygrpkidgel
361 kitsvernsk mdryafldk allickrrgd sydlkdfvnl hsfqvrddss gdrdnkkwsh
421 mflledqga qgyelffkr elkkkwmeqf emaisniype natanghdfq mfsfeettsc
481 kacqmllrgt fyqgyrchrcrasahkeclg rvppcgrhgq dfpgtmkdkd lhrraqdkkr
541 nelglpkmev fqeyyglppp pgaigpflrl npgdivelrk aaeqnwweg mtstneigw
601 fpcnrvkpyv hgppqdlsvh lwyagpmera gaesilanrs dgflvrqrv kdaefaisi
661 kynvevkhtv kimtaeglyr itekkafrgl telvefyqqn slkdcfksld titqfpfkep
721 ekrtisrpav gstkyftak arydfcardr selslkegdi ikilnkkqq gwwrgeiygr
781 vgwfrpanyve edyseyc

Human Vav Amino Acid Sequence (1-797)

Figure 11B

1 gaattcggg ccggtatgc cggcggcggc ggccggcggc gcggcggcgg cggcgggag
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 121 ccgctgggc tccgccctg cccaggccat ggccggcaac gtaagaaga gctctgggc
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Human Cbl Nucleotide Sequence (1-3090)

Figure 12A

1 magnvkkssg agggsgsgsg aggliglmkd afqphhhhhh lshppctvd kkmvekcwkl
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541 pqrtpcpctp gdcpsrdklp pvpssrpgds wlsrtipkvp vatpnpgdpw ngreltnrht
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721 eamytisqa lsvaensag egnlatahts tgpeesened dgydvkppv pavlartrls
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Human Cbl Amino Acid Sequence (1-896)

Figure 12B

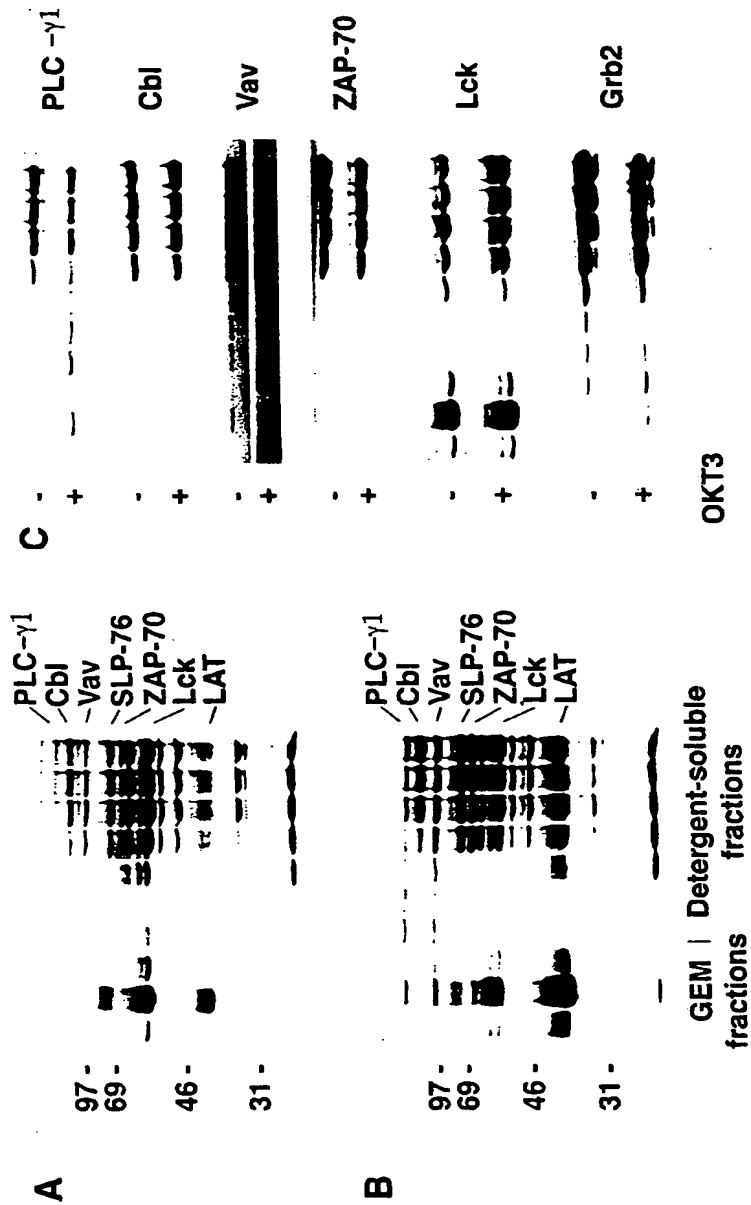


Fig. 13

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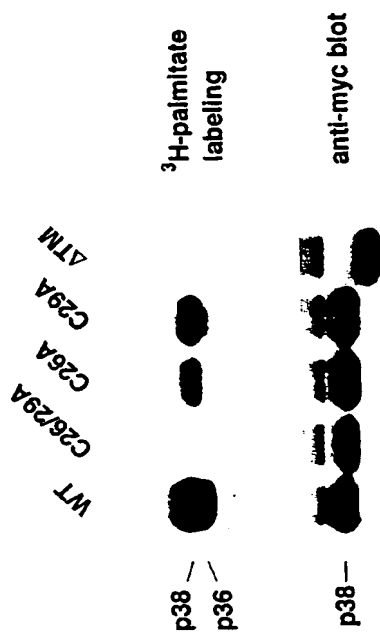


Fig. 14

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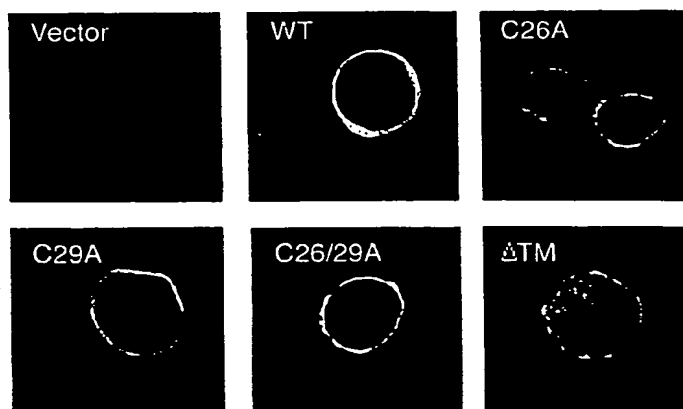
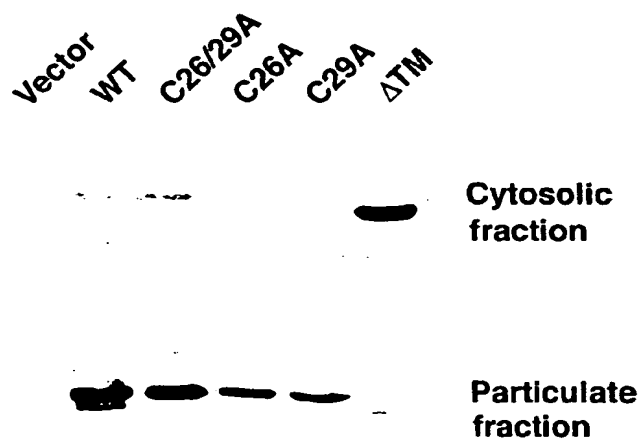
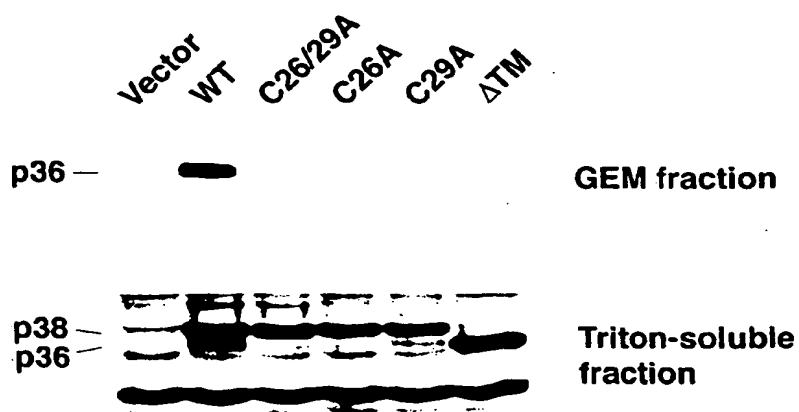
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FIG. 15

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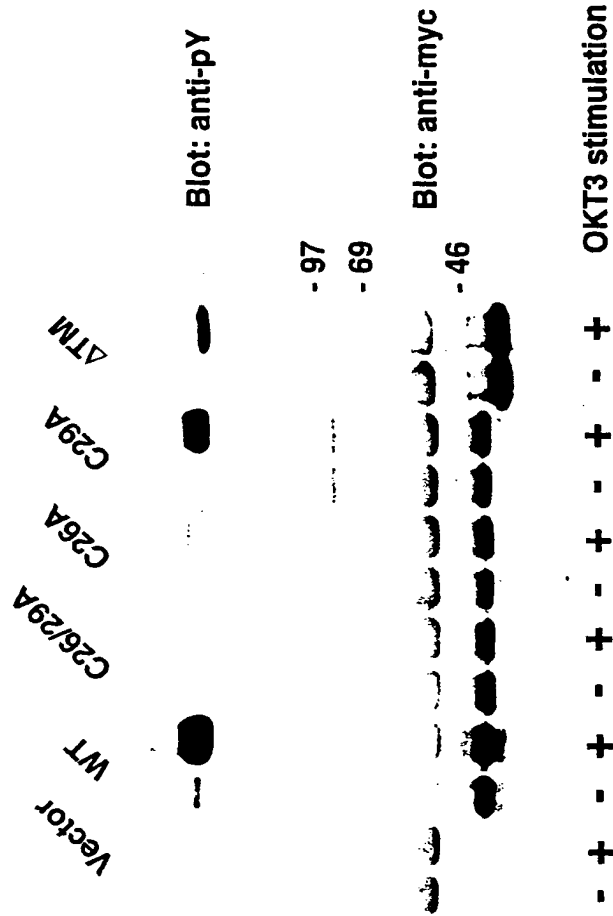


Fig. 16

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SEQUENCE LISTING

<110> Samelson, Lawrence E.
Zhang, Weiguo

<120> Compositions and Methods for Identifying and Testing
Tyrosine Kinase Substrates and Their Agonists and
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<130> NIH-05033

<140> Unknown
<141> 1998-12-23

<150> 60/068,690
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<p>1999-418926/35 B04 D16 USSH 1997.12.23 US DEPT HEALTH & HUMAN SERVICES *WO 09932627-A2 1997.12.23 1997-068690(+1997US-068690) (1999.07.01) C12N 15/12, C07K 14/705, C12N 15/62, G01N 33/50, 33/53, C12Q 1/68, C07K 16/28 Linker for activation of T cell protein used to, e.g. screen for modulators of T cell signaling (Eng) C1999-123167 N(AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW) Addnl. Data: SAMELSON L E, ZHANG W 1998.12.23 1998WO-US27400</p>	<p>B(4-C1G, 4-E2F, 4-G1, 4-N2A, 14-A1, 14-C3, <u>14-G2A</u>, <u>14-G3</u>, 14-H1) D(5-H9, 5-H11, 5-H12A, 5-H12D2, 5-H17A6) .8</p> <p>(I) comprises at least part of the 233 amino acid (aa) sequence (S1) (given in the specification), of the human LAT (linker for activation of T cells) protein. INDEPENDENT CLAIMS are also included for the following: (1) a purified antibody (Ab) that binds specifically to (I); (2) isolated nucleic acid (II) that encodes (S1), or its complement; (3) method of screening compounds for modulation of interaction between (I) and a LAT-binding ligand; (4) method for detecting (I) by reaction with Ab; and (5) method for detecting (II) by hybridization.</p> <p>ACTIVITY Immunomodulatory; antimicrobial; anticancer; anti-inflammatory; anti-allergic.</p>
<p>NOVELTY Isolated polypeptide (I) comprises a part the human LAT (linker for activation of T cells) protein sequence.</p> <p>DETAILED DESCRIPTION</p>	<p>MECHANISM OF ACTION Modulation of interaction between (I) and the T-cell receptor (TCR) affects the TCR signaling pathway. LAT is a substrate for</p> <p style="text-align: right;"> WO 09932627-A+</p>

<p>tyrosine kinases and becomes phosphorylated after TCR engagement, resulting in recruitment of other signaling molecules.</p> <p>USE (I) is used to identify and test (ant)agonists of tyrosine kinase signaling pathways, i.e. modulation of interaction between tyrosine kinase substrates and intracellular ligands or between these ligands and other members of the pathway, including identification of downstream signaling proteins, particularly in immune system cells. These modulators are potentially useful as drugs and diagnostic agents, particularly for diseases that involve undesirable cell growth, differentiation, proliferation or T cell anergy, e.g. neoplasia, inflammation, hypersensitivity/allergy, microbial infection, metabolic, genetic or autoimmune diseases, graft rejection. (I) is also used to generate specific antibodies, used for detection of LAT. Nucleic acid (II) that encodes (I), or its fragments, are used to identify homologous sequences in other species; to detect the LAT gene and as sources of antisense therapeutics.</p> <p>ADVANTAGE Modulators of (I) are potentially more specific and less toxic than known immunosuppressants such as cyclosporin.</p>	<p>ADMINISTRATION Modulators of (I) are administered parenterally, e.g. at 10-1000 µg/kg.</p> <p>EXAMPLE cDNA encoding human LAT (linker for activation of T cells) protein was fused to a myc tag-encoding sequence, then cloned into pcDNA3 for transfection of 293T cells. Immunoblotting with the anti-myc antibody 9E10 indicated presence of a 40 kDa protein in transfected cells only, showing that the cDNA contained the entire coding region.</p> <p>TECHNOLOGY FOCUS Biotechnology - Preferred Polypeptides: (I) includes at least one tyrosine residue and is particularly aa 28-233 (the cytosolic domain). (S1) has 10 tyrosine residues in the predicted cytosolic domain and 5 potential binding sites for the Grb2 SH2 domain. Preferred Nucleic Acid: (S1) is encoded by a 1059 bp sequence (S2) (given in the specification), and this may be part of an expression vector, optionally present inside a host cell.</p> <p style="text-align: right;"> WO 09932627-A+/1</p>
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<p>1999-418926/35</p> <p>Preparation: LAT was purified from Jurkat E6.1 cells that had been stimulated with OKT3 ascites, then digested with trypsin and peptide fragments sequenced. The information obtained was used to search the GenBank database and an expressed sequence tag clone (from human fetal heart) identified. A fragment of this clone was used to screen a cDNA library from YT cells and a 1.6 kb fragment identified. It included an open reading frame for (4). LAT mRNA is detected mainly in the thymus and peripheral blood, and at a low level in the spleen. Once isolated, the cDNA can be expressed in vitro or cloned into conventional expression vectors. Biology - Preferred Methods: In method (3), (I), which can bind a LAT-binding ligand (L); (L) and at least one test compound are incubated together and the extent of (I)-(L) binding measured. Particularly (L) is a tyrosine kinase, specifically ZAP-70 or Syk, and (I) is particularly part of a fusion protein. In method (4), Ab is mono- or poly-clonal and the test sample includes lymphocytes. In method (5), the test material is RNA or DNA, particularly from lymphocytes, and detection of a hybridization complex is correlated with expression of the LAT gene in these cells. Preparation: Ab are produced by conventional immunization with LAT</p>	<p>(or its mutants, fragments) and/or cell fusion methods. Organic Chemistry - Preparation: Fragments of LAT, and oligonucleotide fragments of (II), are produced by usual methods of chemical synthesis. (124pp1251DwgNo.0/16)</p> <p style="text-align: right;"> WO 09932627-A/2</p>
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ID AAX89078 standard; DNA; 2758 BP.
XX
AC AAX89078;
XX
DT 14-SEP-1999 (first entry)
XX
DE Nucleotide sequence of human Vav.
XX
KW LAT; tyrosine kinase; linker for activation of T cell; TCR; human;
KW T-cell receptor; TCR signalling pathway; neoplasia; inflammation;
KW hypersensitivity; allergy; microbial infection; genetic disease;
KW autoimmune disease; graft rejection; modulator; Vav; ss.
XX
OS Homo sapiens.
XX
PN WO9932627-A2.
XX
PD 01-JUL-1999.
XX
PF 23-DEC-1998; 98WO-US27400.
XX
PR 23-DEC-1997; 97US-0068690.
XX
PA (USSH) US DEPT HEALTH & HUMAN SERVICES.
XX
PI Samelson LE, Zhang W;
XX
DR WPI; 1999-418926/35.
DR P-PSDB; AAY27125.
XX
PT Linker for activation of T cell protein used to, e.g. screen for
PT modulators of T cell signalling
XX
PS Disclosure; Fig 11A; 125pp; English.

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12 (US)

ID AAY27125 standard; Protein; 797 AA.
 XX
 AC AAY27125;
 XX
 DT 14-SEP-1999 (first entry)
 XX
 DE Amino acid sequence of human Vav.
 XX
 KW LAT; tyrosine kinase; linker for activation of T cell; TCR; human;
 KW T-cell receptor; TCR signalling pathway; neoplasia; inflammation;
 KW hypersensitivity; allergy; microbial infection; genetic disease;
 KW autoimmune disease; graft rejection; modulator; Vav.
 XX
 OS Homo sapiens.
 XX
 PN WO9932627-A2.
 XX
 PD 01-JUL-1999.
 XX
 PF 23-DEC-1998; 98WO-US27400.
 XX
 PR 23-DEC-1997; 97US-0068690.
 XX
 PA (USSH) US DEPT HEALTH & HUMAN SERVICES.
 XX
 PI Samelson LE, Zhang W;
 XX
 DR WPI; 1999-418926/35.
 DR N-PSDB; AAX89078.
 XX
 PT Linker for activation of T cell protein used to, e.g. screen for
 PT modulators of T cell signalling
 XX
 PS Disclosure; Fig 11B; 125pp; English.
 XX
 CC The invention relates to a protein tyrosine kinase substrate LAT (linker
 CC for activation of T cells) protein. Modulation of interaction between LAT
 CC and the T-cell receptor (TCR) affects the TCR signalling pathway. LAT is
 CC a substrate for tyrosine kinases and becomes phosphorylated after TCR
 CC engagement, resulting in recruitment of other signalling molecules. LAT
 CC is used to identify and test (ant)agonists of tyrosine kinase signalling
 CC pathways, i.e. modulation of interaction between tyrosine kinase
 CC substrates and intracellular ligands or between these ligands and other
 CC members of the pathway, including identification of downstream signalling
 CC proteins, particularly in immune system cells. These modulators are
 CC potentially useful as drugs and diagnostic agents, particularly for
 CC diseases that involve undesirable cell proliferation, differentiation,
 CC growth or T cell anergy, e.g. neoplasia, inflammation, hypersensitivity/
 CC allergy, microbial infection, metabolic, genetic or autoimmune diseases,
 CC graft rejection. LAT is also used to generate specific antibodies, used
 CC for detection of LAT. Nucleic acid that encodes LAT, or its fragments,
 CC are used to identify homologous sequences in other species; to detect the
 CC LAT gene and as sources of antisense therapeutics. Modulators of LAT are
 CC potentially more specific and less toxic than known immunosuppressants
 CC such as cyclosporin. The present sequence represents the amino acid
 CC sequence of human Vav.
 XX
 SQ Sequence 797 AA;
 SQ 54 A; 56 R; 29 N; 50 D; 0 B; 21 C; 37 Q; 70 E; 0 Z; 51 G; 16 H;
 SQ 38 I; 66 L; 57 K; 18 M; 41 F; 35 P; 44 S; 37 T; 12 W; 32 Y; 33 V;
 SQ 0 Others;
 mnvsywaiwt renasakrkq flclknirtf lstccekfgl krselifeafd lfdvqdfgkv
 iytlasalawt piaqnrngimp fpteesvgd ediyglsdq iddtveeded lydcveneea
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kitsverrrsk mdryaflldk allickrrgd sydlkdfvn1 hsfqvrddss gdrdnkkwsh
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